09/884,526

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DB=PGPB,USPT; PLUR=YES; OP=AND			
L5	l2 and L4	11	L5
L4	(reduc$ or decreas$ or diminish$ or inhibit$) near7 (globotriaosylceramide or gb3)	17	L4
L3	l1 and L2	7	L3
L2	galactosidase	29978	L2
L1	(reduc$ or decreas$) near7 (globotriaosylceramide or gb3)	11	L1

END OF SEARCH HISTORY

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Search Results - Record(s) 1 through 11 of 11 returned.

☐ 1. 20040110935. 29 Jul 03. 10 Jun 04. Universal carrier for targeting molecules to Gb3 receptor expressing cells. Johannes, Ludger, et al. 530/395; 536/23.1 C07H021/04 C07K014/00.

☐ 2. 20040033217. 28 May 03. 19 Feb 04. Intraperitoneal delivery of genetically engineered mesenchymal stem cells. Vanguri, Padmavathy, et al. 424/93.21; 435/366 A61K048/00 C12N005/08.

☐ 3. 20030119874. 26 Nov 02. 26 Jun 03. Method for enhancing mutant enzyme activity in gaucher disease. Fan, Jian-Qiang, et al. 514/317; 514/328 A61K031/445.

☐ 4. 20020095135. 19 Jun 01. 18 Jul 02. Combination enzyme replacement, gene therapy and small molecule therapy for lysosomal storage diseases. Meeker, David, et al. 604/522; A61M031/00.

☐ 5. 20020035072. 07 Sep 01. 21 Mar 02. Method for enhancing mutant enzyme activities in lysosomal storage disorders. Fan, Jian-Qiang, et al. 514/25; 514/277 514/28 514/281 514/315 A61K031/70 A61K031/435 A61K031/445.

☐ 6. 20020012658. 16 Jun 99. 31 Jan 02. PREVENTION AND TREATMENT OF VEROTOXIN-INDUCED DISEASE. WILLIAMS, JAMES A., et al. 424/93.2; A61K048/00 A01N063/00.

☐ 7. 6652857. 16 Jun 99; 25 Nov 03. Methods for producing avian verotoxin antitoxin. Williams; James A., et al. 424/169.1; 424/130.1 424/150.1 436/547. A61K039/40 A61K039/395 G01N033/53.

☐ 8. 6599919. 07 Sep 01; 29 Jul 03. Method for enhancing mutant enzyme activities in lysosomal storage disorders. Fan; Jian-Qiang, et al. 514/315; 435/208. A61K031/445.

☐ 9. 6583158. 26 Jun 00; 24 Jun 03. Method for enhancing mutant enzyme activities in lysosomal storage disorders. Fan; Jian-Qiang, et al. 514/315; 424/94.61 435/206 435/208 514/25 514/277 514/28 514/281. A61K031/445 A61K031/70 A61K031/435.

☐ 10. 6413768. 02 Dec 98; 02 Jul 02. Expression plasmids. Galen; James E.. 435/320.1; 530/300 530/350 530/403 536/24.1. C12N015/63.

☐ 11. 6080400. 13 Mar 97; 27 Jun 00. Compositions for the prevention and treatment of verotoxin-induced disease. Williams; James A., et al. 424/93.2; 424/241.1 424/93.4 424/93.48. A01N063/00 A61K039/108.

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Terms	Documents
L2 and L4	11

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09/884,526

=> d his

(FILE 'HOME' ENTERED AT 15:10:36 ON 20 AUG 2004)

FILE 'MEDLINE, CAPLUS, BIOSIS, SCISEARCH' ENTERED AT 15:10:47 ON 20 AUG 2004

L1 252 S (REDUC? OR DECREAS? OR INHIBIT? OR DIMINISH?)(7A)(GLOBOTRIAOS
L2 91764 S GALACTOSIDASE
L3 14 S L1(8A)L2
L4 7 DUP REM L3 (7 DUPLICATES REMOVED)
L5 184 S (REDUC? OR DECREAS? OR INHIBIT? OR DIMINISH?)(7A)(GB3 OR GL3
L6 11 S L2(S)L5
L7 35 S L2 AND L5
L8 261 S (REDUC? OR DECREAS? OR INHIBIT? OR DIMINISH?)(7A)(GB3 OR GL3
L9 32 S L2(S)L8
L10 80 S L2 AND L8
L11 17 DUP REM L9 (15 DUPLICATES REMOVED)
L12 31 DUP REM L10 (49 DUPLICATES REMOVED)

=> d au ti so pi ab 1-17 l11

L11 ANSWER 1 OF 17 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AU Ziegler R J; Lonning S M; Armentano D; Li C; Souza D W; Cherry M; Ford C; Barbon C M; Desnick R J; Gao G P; Wilson J M; Peluso R; Godwin S; Carter B J; Gregory R J; Wadsworth S C; Cheng S H (Reprint)
TI AAV2 vector harboring a liver-restricted promoter facilitates sustained expression of therapeutic levels of alpha-galactosidase A and the induction of immune tolerance in Fabry mice
SO MOLECULAR THERAPY, (FEB 2004) Vol. 9, No. 2, pp. 231-240.
Publisher: ACADEMIC PRESS INC ELSEVIER SCIENCE, 525 B ST, STE 1900, SAN DIEGO, CA 92101-4495 USA.
ISSN: 1525-0016.
AB The successful application of gene therapy for the treatment of genetic diseases such as Fabry is reliant on the development of vectors that are safe and that facilitate sustained expression of therapeutic levels of the transgene product. Here, we report that intravenous administration of a recombinant AAV2 vector encoding human alpha-**galactosidase** A under the transcriptional control of a liver-restricted enhancer/promoter (AAV2/DC190-alphagal) generated significantly higher levels of expression in BALB/c and Fabry mice than could be realized using the ubiquitous CMV promoter (AAV2/CMVHI-alphagal). Moreover, AAV2/DC190-alphagal-mediated hepatic expression of alpha-**galactosidase** A was sustained for 12 months in BALB/c mice and was associated with a significantly reduced immune response to the expressed enzyme. Subsequent challenge of the AAV2/DC190-alphagal-treated animals with recombinant human alpha-**galactosidase** A at 6 months failed to elicit the production of anti-alpha-**galactosidase** A antibodies, suggesting the induction of immune tolerance in these animals. The levels of expression attained with AAV2/DC190-alphagal in the Fabry mice were sufficient to **reduce** the abnormal accumulation of **globotriaosylceramide** in the liver, spleen, and heart to basal levels and in the kidney by approximately 40% at 8 weeks. Together, these results demonstrate that AAV2-mediated gene transfer that limits the expression of alpha-**galactosidase** A to the liver may be a viable strategy for treating Fabry disease.

L11 ANSWER 2 OF 17 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AU Baehner F; Kampmann C; Whybra C; Miebach E; Wiethoff C M; Beck M (Reprint)
TI Enzyme replacement therapy in heterozygous females with Fabry disease: Results of a phase IIIB study
SO JOURNAL OF INHERITED METABOLIC DISEASE, (NOV 2003) Vol. 26, No. 7, pp. 617-627.
Publisher: KLUWER ACADEMIC PUBL, VAN GODEWIJCKSTRAAT 30, 3311 GZ DORDRECHT, NETHERLANDS.

ISSN: 0141-8955.

AB Fabry disease is an X-linked glycosphingolipid storage disorder caused by a deficiency of alpha-**galactosidase** A. Affected patients experience debilitating neuropathic pain and have premature mortality due to renal failure, cardiovascular disease or cerebrovascular complications. The disease may be X-linked dominant, sincemost females heterozygous for Fabry disease are affected clinically. We evaluated the safety, efficacy and pharmacokinetics of agalsidase alfa (Replagal) administered intravenously to female patients with Fabry disease in an open-label, single-centre study. Fifteen severely affected patients received agalsidase alfa at 0.2 mg/kg every other week for up to 55 weeks. Agalsidase alfa was safe and well-tolerated in female patients. None of the patients developed antibodies or experienced an infusion reaction to agalsidase alfa. The pharmacokinetic profile of agalsidase alfa in female patients is comparable to the pharmacokinetics of agalsidase alfa in male patients. Mean urine sediment and plasma **Gb3** levels **decreased** from baseline at 13, 27 and 41 weeks. A significant decrease in left ventricular mass from baseline was seen at weeks 27 ($p = 0.003$) and 41 ($p = 0.039$), and a significant reduction in QRS durations was seen at week 27 ($p = 0.007$). Furthermore, there was a significant improvement in quality of life. Renal function did not deteriorate in these 15 female patients over the 13- to 41-week period of observation. We conclude that enzyme replacement therapy with agalsidase alfa was safe and effective in female patients heterozygous for Fabry disease.

L11 ANSWER 3 OF 17 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

AU Eitzman D T (Reprint); Bodary P F; Shen Y C; Khairallah C G; Wild S R; Abe A; Shaffer-Hartman J; Shayman J A

TI Fabry disease in mice is associated with age-dependent susceptibility to vascular thrombosis

SO JOURNAL OF THE AMERICAN SOCIETY OF NEPHROLOGY, (FEB 2003) Vol. 14, No. 2, pp. 298-302.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA.
ISSN: 1046-6673.

AB Fabry disease is an X-linked lysosomal storage disorder due to deficiency of a-**galactosidase** A (GLA) activity that results in the widespread accumulation of neutral glycosphingolipids. Renal failure, neuropathy, premature myocardial infarction, and stroke occur in patients with this condition primarily due to deposition of glycosphingolipids in vascular endothelial cells. The clinical consequences of Fabry disease suggest that vascular thrombosis may play a prominent role in the pathogenesis of this disease; however, the vasculopathy associated with Fabry disease has not been extensively studied. To determine if mice genetically deficient in Gla are susceptible to vascular thrombosis, a photochemical carotid injury model was used to induce occlusive thrombosis. In this model, Gla-/0 mice displayed a progressive age-dependent shortening of the time to occlusive thrombosis after vascular injury that correlated with progressive accumulation of globotriasylceramide (Gb3) in the arterial wall. Bone marrow transplantation from Gla-/0 to Gla+/0 mice and from Gla+/0 to Gla-/0 mice did not change the thrombotic phenotype of the host. These studies reveal a potent vascular prothrombotic phenotype in Gla-deficient mice and suggest that antithrombotic therapies as well as therapies designed to **reduce** the vascular accumulation of **Gb3** may have beneficial effects on thrombotic complications in patients with Fabry disease.

L11 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN

AU Hughes, Alisa K.; Ergonul, Zuhal; Stricklett, Peter K.; Kohan, Donald E.

TI Molecular basis for high renal cell sensitivity to the cytotoxic effects of shigatoxin-1: upregulation of globotriaosylceramide expression. [Erratum to document cited in CA137:334170]

SO Journal of the American Society of Nephrology (2003), 14(5), No pp. given

CODEN: JASNEU; ISSN: 1046-6673
AB The name of the second author, Z. Ergonul, was misspelled.

L11 ANSWER 5 OF 17 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AU Takahashi H; Hirai Y; Migita M; Seino Y; Fukuda Y; Sakuraba H; Kase R; Kobayashi T; Hashimoto Y; Shimada T (Reprint)
TI Long-term systemic therapy of Fabry disease in a knockout mouse by adeno-associated virus-mediated muscle-directed gene transfer
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (15 OCT 2002) Vol. 99, No. 21, pp. 13777-13782.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA.
ISSN: 0027-8424.
AB Fabry disease is a systemic disease caused by genetic deficiency of a lysosomal enzyme, alpha-**galactosidase** A (alpha-gal A), and is thought to be an important target for enzyme replacement therapy. We studied the feasibility of gene-mediated enzyme replacement for Fabry disease. The adeno-associated virus (AAV) vector containing the alpha-gal A gene was injected into the right quadriceps muscles of Fabry knockout mice. A time course study showed that alpha-gal A activity in plasma was increased to approximate to25% of normal mice and that this elevated activity persisted for up to at least 30 weeks without development of anti-alpha-gal A antibodies. The alpha-gal A activity in various organs of treated Fabry mice remained 5-20% of those observed in normal mice. Accumulated globotriaosylceramide in these organs was completely cleared by 25 weeks after vector injection. **Reduction** of **globotriaosylceramide** levels was also confirmed by immunohistochemical and electron microscopic analyses. Echocardiographic examination of treated mice demonstrated structural improvement of cardiac hypertrophy 25 weeks after the treatment. AAV vector-mediated muscle-directed gene transfer provides an efficient and practical therapeutic approach for Fabry disease.

L11 ANSWER 6 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
AU Hughes, Alisa K.; Ergonal, Zuhal; Stricklett, Peter K.; Kohan, Donald E.
TI Molecular basis for high renal cell sensitivity to the cytotoxic effects of shigatoxin-1: upregulation of globotriaosylceramide expression
SO Journal of the American Society of Nephrology (2002), 13(9), 2239-2245
CODEN: JASNEU; ISSN: 1046-6673
AB Cellular injury in post-diarrheal hemolytic-uremic syndrome (D+HUS) is related to shigatoxin (Stx) binding to globotriaosylceramide (Gb3). High renal Gb3 expression may determine renal susceptibility in D+HUS; however, the mol. mechanism(s) responsible for such relatively abundant Gb3 levels are unknown. Consequently, kidney cells expressing high Gb3 (cultured human proximal tubule cells [HPT]) were compared with non-kidney cells with low Gb3 content (cultured human brain microvascular endothelial cells [HBEC]). HPT were much more sensitive to the cytotoxic and protein synthesis inhibitory effects of Stx-1; this correlated with Gb3 content and 125I-Stx-1 binding. HPT had greater Gb3 synthase (GalT6) and lower α-galactosidase activities than HBEC, whereas lactosylceramide synthase (GalT2) activity was higher in HBEC. Ceramide glucosyltransferase (CGT) activity was similar between the two cell types. The higher HPT GalT6 activity was associated with increased GalT6 mRNA steady-state levels, but no difference in GalT6 mRNA half-life. The lower HPT α-galactosidase activity was associated with reduced α-galactosidase mRNA steady-state levels but no difference in α-galactosidase mRNA half-life. Higher HBEC GalT2 activity was associated with increased steady-state GalT2 mRNA levels. These studies suggest that high renal Gb3 expression is due to enhanced GalT6 gene transcription and reduced α-galactosidase gene transcription and occur despite relatively low GalT2 activity.

L11 ANSWER 7 OF 17 MEDLINE on STN DUPLICATE 2
AU Asfaw Befekadu; Ledvinova Jana; Dobrovolny Robert; Bakker Henk D; Desnick

Robert J; van Diggelen Otto P; de Jong Jan G N; Kanzaki Tamotsu; Chabas Amparo; Maire Irene; Conzelmann Ernst; Schindler Detlev

TI Defects in degradation of blood group A and B glycosphingolipids in Schindler and Fabry diseases.

SO Journal of lipid research, (2002 Jul) 43 (7) 1096-104.
Journal code: 0376606. ISSN: 0022-2275.

AB Skin fibroblast cultures from patients with inherited lysosomal enzymopathies, alpha-N-acetylgalactosaminidase (alpha-NAGA) and alpha-galactosidase A deficiencies (Schindler and Fabry disease, respectively), and from normal controls were used to study in situ degradation of blood group A and B glycosphingolipids. Glycosphingolipids A-6-2 (GalNAc (alpha 1-->3)[Fuc alpha 1-->2]Gal(beta1-->4)GlcNAc(beta 1-->3)Gal(beta 1--> 4)Glc (beta 1-->1')Cer, IV(2)-alpha-fucosyl-IV(3)-alpha-N-acetylgalactosaminylneolactotetraosylceramide), B-6-2 (Gal(alpha 1-->3)[Fuc alpha 1--> 2] Gal (beta 1-->4)GlcNAc(beta 1-->3)Gal(beta 1-->4)Glc(beta 1-->1')Cer, IV(2)- alpha-fucosyl-IV(3)-alpha-galactosylneolactotetraosylceramide), and globoside (GalNAc(beta 1-->3)Gal(alpha 1-->4)Gal(beta 1-->4)Glc(beta 1-->1') Cer, globotetraosylceramide) were tritium labeled in their ceramide moiety and used as natural substrates. The degradation rate of glycolipid A-6-2 was very low in fibroblasts of all the alpha-NAGA-deficient patients (less than 7% of controls), despite very heterogeneous clinical pictures, ruling out different residual enzyme activities as an explanation for the clinical heterogeneity. Strongly elevated urinary excretion of blood group A glycolipids was detected in one patient with blood group A, secretor status (five times higher than upper limit of controls), in support of the notion that blood group A-active glycolipids may contribute as storage compounds in blood group A patients. When glycolipid B-6-2 was fed to alpha-**galactosidase** A-deficient cells, the degradation rate was surprisingly high (50% of controls), while that of **globotriaosylceramide** was **reduced** to less than 15% of control average, presumably reflecting differences in the lysosomal enzymology of polar glycolipids versus less-polar ones. Relatively high-degree degradation of substrates with alpha-D-Galactosyl moieties hints at a possible contribution of other enzymes.

L11 ANSWER 8 OF 17 MEDLINE on STN DUPLICATE 3

AU Sessa Adalberto; Meroni Mietta; Battini Graziana; Maglio Alessia; Nebuloni Manuela; Tosoni Angela; Panichi Vincenzo; Bertagnolio Barbara

TI Renal transplantation in patients with Fabry disease.

SO Nephron, (2002 Jun) 91 (2) 348-51.
Journal code: 0331777. ISSN: 0028-2766.

AB Anderson-Fabry disease (AFd) is a rare X-linked disorder characterized by deficiency of alpha-galactosidase A that leads to systemic accumulation of neutral glycosphingolipids, predominantly globotriaosylceramide (Gb3), in body fluids and visceral tissues, including the kidney. End-stage renal failure is a common manifestation in hemizygous males that often occurs by the third to fourth decade of life. Usually transplanted patients exhibit improvement in clinical symptoms of the disease, probably related to the production of alpha-**galactosidase** A from the grafted kidney, but mainly related to the increase in Gb3 clearance by the functioning kidney, and increased survival of red cells due to the correction of the uremic status with an evident **decrease** in the production of **Gb3** depending from hemolysis. Several Fabry patients with successful kidney graft survived for 10-15 years and died for cardiovascular complications related to the metabolic disease. The loss of grafted kidney is due to rejection, thrombosis or sepsis. An important issue considering renal transplantation in AFd is the recurrence of the disease in the kidney graft; however, no evidence regarding this possibility has occurred up to now. We report herein the ultrastructural study of the urinary sediment of a 35-year-old male Fabry patient with a severe clinical form of the disease with progression to ESRF at age 29, and submitted to renal transplantation at 33 years. Ultrastructural findings of the urinary sediment documented several cells, probably tubular epithelial cells, with

typical accumulation of myelinic bodies resulting from intracellular storage of neutral glycosphingolipids. This morphological evidence arises the problem of the possible recurrence of AFd in the kidney graft in patients with severe phenotype of the metabolic disease.

L11 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN
AU Branton, Mary H.; Schiffmann, Raphael; Sabnis, Sharda G.; Murray, Gary J.; Quirk, Jane M.; Altarescu, Gheona; Goldfarb, Lev; Brady, Roscoe O.; Balow, James E.; Austin, Howard A., III; Kopp, Jeffrey B.
TI Natural history of Fabry renal disease: Influence of α-galactosidase A activity and genetic mutations on clinical course
SO Medicine (Baltimore, MD, United States) (2002), 81(2), 122-138
CODEN: MEDIAV; ISSN: 0025-7974
AB We discuss the medical records of 105 male patients with Fabry disease. We describe the clin. course and histol. of their renal disease and correlate them with residual α-galactosidase A (α gal A) activity and with mutations in the α-gal A gene. Hemizygous male patients with Fabry disease may develop proteinuria and chronic renal insufficiency in adolescence or early adulthood. By age 35 yr, 50% of patients had non-nephrotic range proteinuria and almost 20% had early renal insufficiency. 50% Of surviving patients had renal insufficiency by age 42 yr, and 50% had progressed to end-stage renal disease by age 47 yr. 23% Of all patients eventually developed end-stage renal disease. By age 55 yr, 500% of the patients had died, and all had died by age 60 yr. Nephrotic proteinuria was present in 18% of patients and hypertension was present in 30% of patients. Either manifestation may appear before or after the onset of chronic renal insufficiency. After the onset of chronic renal insufficiency, the mean rate of change in glomerular filtration rate was -12.2 mL/min per yr with patients reaching end-stage renal disease after 4.1 yr. The presence of detectable residual α gal A activity in peripheral leukocytes was associated with a later onset of chronic renal insufficiency, lower renal globotriaosylceramide content, and lower scores for renal histol. damage. Conservative missense mutations were associated with longer renal survival compared with nonconservative missense or other mutations.

L11 ANSWER 10 OF 17 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AU Jung S C; Han I P; Limaye A; Xu R; Gelderman M P; Zerfas P; Tirumalai K; Murray G J; During M J; Brady R O; Qasba P (Reprint)
TI Adeno-associated viral vector-mediated gene transfer results in long-term enzymatic and functional correction in multiple organs of Fabry mice
SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (27 FEB 2001) Vol. 98, No. 5, pp. 2676-2681.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418 USA.
ISSN: 0027-8424.
AB Fabry disease is a lysosomal storage disorder caused by a deficiency of the lysosomal enzyme alpha -**galactosidase** A (alpha -gal A). This enzyme deficiency leads to impaired catabolism of alpha -galactosyl-terminal lipids such as globotriaosylceramide (Gb3). Patients develop painful neuropathy and vascular occlusions that progressively lead to cardiovascular, cerebrovascular, and renal dysfunction and early death. Although enzyme replacement therapy and bone marrow transplantation have shown promise in the murine analog of Fabry disease, gene therapy holds a strong potential for treating this disease in humans. Delivery of the normal alpha -gal A gene (cDNA) into a depot organ such as liver may be sufficient to elicit corrective circulating levels of the deficient enzyme. To investigate this possibility, a recombinant adeno-associated viral vector encoding human alpha -gal A (rAAV-AGA) was constructed and injected into the hepatic portal vein of Fabry mice. Two weeks postinjection, alpha -gal A activity in the livers of rAAV-AGA-injected Fabry mice was 20-35% of that of the normal mice. The transduced animals continued to show higher alpha -gal A levels in liver and other tissues

compared with the untouched Fabry controls as long as 6 months after treatment. In parallel to the elevated enzyme levels, we see significant **reductions** in **Gb3** levels to near normal at 2 and 5 weeks posttreatment. The lower Gb3 levels continued in liver, spleen, and heart, up to 25 weeks with no significant immune response to the virus or alpha -gal A. Also, no signs of liver toxicity occurred after the rAAV-AGA administration. These findings suggest that an AAV-mediated gene transfer may be useful for the treatment of Fabry disease and possibly other metabolic disorders.

L11 ANSWER 11 OF 17 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
AU Abe A (Reprint); Wild S R; Lee L; Shayman J A
TI Agents for the treatment of glycosphingolipid storage disorders
SO CURRENT DRUG METABOLISM, (SEP 2001) Vol. 2, No. 3, pp. 331-338. Publisher: BENTHAM SCIENCE PUBL LTD, PO BOX 1673, 1200 BR HILVERSUM, NETHERLANDS.
ISSN: 1389-2002.
AB We have developed a series of inhibitors of glucosylceramide synthase that are structurally based on the parent compound D-threo-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP). These inhibitors provide useful tools for manipulating glycosphingolipid levels in cells and for elucidating questions associated with A sphingolipid signaling. Recently, two highly active glucosylceramide synthase inhibitors, D-threo-3', 4'-ethylenedioxy-1-phenyl-2-palmitoylamino-3-pyrrolidino-1-propanol and D-threo-4'-hydroxy-1-phenyl-2-palmitoylamino-3-pyrrolidino-1-propanol, were designed, synthesized, and studied. These inhibitors markedly reduced glycosphingolipid levels in MDCK cells without any accumulation of intracellular ceramide and associated growth inhibition. Subsequently, each inhibitor was evaluated for its ability to lower glycolipid levels in virally transformed lymphoblasts from a patient with alpha - **galactosidase** A deficiency. Both compounds significantly reduced neutral glycosphingolipid levels in the lymphoblasts without any morphological changes and growth inhibition. Furthermore, the inhibitors were applied to a mouse knockout model of Fabry disease. **Inhibitor** treatment blocked accumulation of **globotriaosylceramide** (Gb(3)) in the kidney, liver and heart of mice. In contrast to another glucosylceramide synthase inhibitor, N-butyldeoxynojirimycin, this treatment was not associated with any significant change in body weight or organ weight and without immunodepletion. These results suggest that these newest PDMP homologues are promising as therapeutic agents for the treatment of glycosphingolipid storage disorders.

L11 ANSWER 12 OF 17 MEDLINE on STN DUPLICATE 4
AU Eng C M; Guffon N; Wilcox W R; Germain D P; Lee P; Waldek S; Caplan L; Linthorst G E; Desnick R J
TI Safety and efficacy of recombinant human alpha-galactosidase A--replacement therapy in Fabry's disease.
SO New England journal of medicine, (2001 Jul 5) 345 (1) 9-16. Journal code: 0255562. ISSN: 0028-4793.
AB BACKGROUND: Fabry's disease, lysosomal alpha-galactosidase A deficiency, results from the progressive accumulation of globotriaosylceramide and related glycosphingolipids. Affected patients have microvascular disease of the kidneys, heart, and brain. METHODS: We evaluated the safety and effectiveness of recombinant alpha-galactosidase A in a multicenter, randomized, placebo-controlled, double-blind study of 58 patients who were treated every 2 weeks for 20 weeks. Thereafter, all patients received recombinant alpha-galactosidase A in an open-label extension study. The primary efficacy end point was the percentage of patients in whom renal microvascular endothelial deposits of globotriaosylceramide were cleared (reduced to normal or near-normal levels). We also evaluated the histologic clearance of microvascular endothelial deposits of globotriaosylceramide in the endomyocardium and skin, as well as changes in the level of pain and the quality of life. RESULTS: In the double-blind study, 20 of the 29 patients in the recombinant

alpha-galactosidase A group (69 percent) had no microvascular endothelial deposits of globotriaosylceramide after 20 weeks, as compared with none of the 29 patients in the placebo group (P<0.001). Patients in the recombinant alpha-**galactosidase** A group also had **decreased** microvascular endothelial deposits of **globotriaosylceramide** in the skin (P<0.001) and heart (P<0.001). Plasma levels of globotriaosylceramide were directly correlated with clearance of the microvascular deposits. After six months of open-label therapy, all patients in the former placebo group and 98 percent of patients in the former recombinant alpha-galactosidase A group who had biopsies had clearance of microvascular endothelial deposits of globotriaosylceramide. The incidence of most treatment-related adverse events was similar in the two groups, with the exception of mild-to-moderate infusion reactions (i.e., rigors and fever), which were more common in the recombinant alpha-galactosidase A group. IgG seroconversion occurred in 88 percent of patients who received recombinant alpha-galactosidase A. CONCLUSIONS: Recombinant alpha-galactosidase A replacement therapy cleared microvascular endothelial deposits of globotriaosylceramide from the kidneys, heart, and skin in patients with Fabry's disease, reversing the pathogenesis of the chief clinical manifestations of this disease.

L11 ANSWER 13 OF 17 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN

AU Takenaka T; Murray G J; Qin G J; Quirk J M; Ohshima T; Qasba P; Clark K; Kulkarni A B; Brady R O; Medin J A (Reprint)

TI Long-term enzyme correction and lipid reduction in multiple organs of primary and secondary transplanted Fabry mice receiving transduced bone marrow cells

SO PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (20 JUN 2000) Vol. 97, No. 13, pp. 7515-7520.
Publisher: NATL ACAD SCIENCES, 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418.
ISSN: 0027-8424.

AB Fabry disease is a compelling target for gene therapy as a treatment strategy. A deficiency in the lysosomal hydrolase alpha-**galactosidase** A (alpha-gal A; PC 3.2.1.22) leads to impaired catabolism of alpha-galactosyl-terminal lipids such as globotriaosylceramide (Gb3). Patients develop vascular occlusions that cause cardiovascular, cerebrovascular, and renal disease. Unlike for some lysosomal storage disorders, there is limited primary nervous system involvement in Fabry disease. The enzyme defect can be corrected by gene transfer. Overexpression of alpha-gal A by transduced cells results in secretion of this enzyme. Secreted enzyme is available for uptake by nontransduced cells presumably by receptor-mediated endocytosis, Correction of bystander cells may occur locally or systemically after circulation of the enzyme in the blood. In this paper we report studies on long-term genetic: correction in an alpha-gal A-deficient mouse model of Fabry disease. alpha-gal A-deficient bone marrow mononuclear cells (BMMCs) were transduced with a retrovirus encoding alpha-gal A and transplanted into sublethally and lethally irradiated or-gal A-deficient mice. alpha-gal A activity and Gb3 levels were analyzed in plasma, peripheral blood mononuclear cells, BMMCs, liver, spleen, heart, lung, kidney, and brain. Primary recipient animals were followed for up to 26 weeks. BMMCs were then transplanted into secondary recipients. Increased alpha-gal A activity and **decreased Gb3** storage were observed in all recipient groups in all organs and tissues except the brain. These effects occurred even with a low percentage of transduced cells. The findings indicate that genetic correction of bone marrow cells derived from patients with Fabry disease may have utility for phenotypic correction of patients with this disorder.

L11 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 5

AU Abe, Akira; Gregory, Susan; Lee, Lihsueh; Killen, Paul D.; Brady, Roscoe O.; Kulkarni, Ashok; Shayman, James A.

TI Reduction of globotriaosylceramide in Fabry disease mice by substrate deprivation

SO Journal of Clinical Investigation (2000), 105(11), 1563-1571
CODEN: JCINAO; ISSN: 0021-9738

AB We used a potent inhibitor of glucosylceramide synthase to test whether substrate deprivation could lower globotriaosylceramide levels in α-galactosidase A (α-gal A) knockout mice, a model of Fabry disease. C57BL/6 mice treated twice daily for 3 days with D-threo-1-ethylendioxyphenyl-2-palmitoylamino-3-pyrrolidino-propanol (D-t-EtDO-P4) showed a concentration-dependent decrement in glucosylceramide levels in kidney, liver, and spleen. A single i.p. injection of D-t-EtDO-P4 resulted in a 55% reduction in renal glucosylceramide, consistent with rapid renal glucosylceramide metabolism A concentration-dependent decrement in renal and hepatic globotriaosylceramide levels was observed in α-Gal A- males treated for 4 wk with D-t-EtDO-P4. When 8-wk-old α-Gal A- males were treated for 8 wk with 10 mg/kg twice daily, renal globotriaosylceramide fell to below starting levels, consistent with an α-galactosidase A-independent salvage pathway for globotriaosylceramide degradation Complications observed with another glucosylceramide synthase inhibitor, N-butyldeoxynojirimycin, including weight loss and acellularity of lymphatic organs, were not observed with D-t-EtDO-P4. These data suggest that Fabry disease may be amenable to substrate deprivation therapy.

L11 ANSWER 15 OF 17 MEDLINE on STN DUPLICATE 6

AU Schiffmann R; Murray G J; Treco D; Daniel P; Sellos-Moura M; Myers M; Quirk J M; Zirzow G C; Borowski M; Loveday K; Anderson T; Gillespie F; Oliver K L; Jeffries N O; Doo E; Liang T J; Kreps C; Gunter K; Frei K; Crutchfield K; Selden R F; Brady R O

TI Infusion of alpha-**galactosidase** A **reduces** tissue **globotriaosylceramide** storage in patients with Fabry disease.

SO Proceedings of the National Academy of Sciences of the United States of America, (2000 Jan 4) 97 (1) 365-70.
Journal code: 7505876. ISSN: 0027-8424.

AB Fabry disease is a lysosomal storage disorder caused by a deficiency of the lysosomal enzyme alpha-galactosidase A (alpha-gal A). This enzymatic defect results in the accumulation of the glycosphingolipid globotriaosylceramide (Gb(3); also referred to as ceramidetrihexoside) throughout the body. To investigate the effects of purified alpha-gal A, 10 patients with Fabry disease received a single i.v. infusion of one of five escalating dose levels of the enzyme. The objectives of this study were: (i) to evaluate the safety of administered alpha-gal A, (ii) to assess the pharmacokinetics of i.v.-administered alpha-gal A in plasma and liver, and (iii) to determine the effect of this replacement enzyme on hepatic, urine sediment and plasma concentrations of Gb(3). alpha-Gal A infusions were well tolerated in all patients. Immunohistochemical staining of liver tissue approximately 2 days after enzyme infusion identified alpha-gal A in several cell types, including sinusoidal endothelial cells, Kupffer cells, and hepatocytes, suggesting diffuse uptake via the mannose 6-phosphate receptor. The tissue half-life in the liver was greater than 24 hr. After the single dose of alpha-gal A, nine of the 10 patients had significantly reduced Gb(3) levels both in the liver and shed renal tubular epithelial cells in the urine sediment. These data demonstrate that single infusions of alpha-gal A prepared from transfected human fibroblasts are both safe and biochemically active in patients with Fabry disease. The degree of substrate reduction seen in the study is potentially clinically significant in view of the fact that Gb(3) burden in Fabry patients increases gradually over decades. Taken together, these results suggest that enzyme replacement is likely to be an effective therapy for patients with this metabolic disorder.

L11 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN

AU Ziegler, Robin J.; Yew, Nelson S.; Li, Chester; Cherry, Maribeth;

Berthelette, Patricia; Romanczuk, Helen; Ioannou, Yiannis A.; Zeidner, Kenneth M.; Desnick, Robert J.; Cheng, Seng H.

TI Correction of enzymatic and lysosomal storage defects in Fabry mice by adenovirus-mediated gene transfer

SO Human Gene Therapy (1999), 10(10), 1667-1682
CODEN: HGTHE3; ISSN: 1043-0342

AB Fabry disease is a recessive, X-linked disorder caused by a deficiency of the lysosomal hydrolase α-galactosidase A. Deficiency of this enzyme results in progressive deposition of the glycosphingolipid globotriaosylceramide (GL-3) in the vascular lysosomes, with resultant distension of the organelle. The demonstration of a secretory pathway for lysosomal enzymes and their subsequent recapture by distant cells through the mannose 6-phosphate receptor pathway has provided a rationale for somatic gene therapy of lysosomal storage disorders. Toward this end, recombinant adenoviral vectors encoding human α-galactosidase A (Ad2/CEHα-Gal, Ad2/CMVHIα-Gal) were constructed and injected i.v. into Fabry knockout mice. Administration of Ad2/CEHα-Gal to the Fabry mice resulted in an elevation of α-galactosidase A activity in all tissues, including the liver, lung, kidney, heart, spleen, and muscle, to levels above those observed in normal animals. However, enzymic expression declined rapidly such that by 12 wk, only 10% of the activity observed on day 3 remained. α-Galactosidase A detected in the plasma of injected animals was in a form that was internalized by Fabry fibroblasts grown in culture. Such internalization occurred via the mannose 6-phosphate receptors. Importantly, concomitant with the increase in enzyme activity was a significant reduction in GL-3 content in all tissues to near normal levels for ≤6 mo posttreatment. However, as expression of α-galactosidase A declined, low levels of GL-3 reaccumulated in some of the tissues at 6 mo. For protracted treatment, the authors showed that readministration of recombinant adenovirus vectors could be facilitated by transient immunosuppression using a monoclonal antibody against CD40 ligand (MR1). Together, these data demonstrate that the defects in α-galactosidase A activity and lysosomal storage of GL-3 in Fabry mice can be corrected by adenovirus-mediated gene transfer. This suggests that gene replacement therapy represents a viable approach for the treatment of Fabry disease and potentially other lysosomal storage disorders.

L11 ANSWER 17 OF 17 MEDLINE on STN DUPLICATE 7

AU Mobassaleh M; Gross S K; McCluer R H; Donohue-Rolfe A; Keusch G T

TI Quantitation of the rabbit intestinal glycolipid receptor for Shiga toxin. Further evidence for the developmental regulation of globotriaosylceramide in microvillus membranes.

SO Gastroenterology, (1989 Aug) 97 (2) 384-91.
Journal code: 0374630. ISSN: 0016-5085.

AB Shiga toxin, produced by Shigella dysenteriae 1, causes enterotoxic, cytotoxic, and neurotoxic effects, which may be mediated by a glycolipid receptor, globotriaosylceramide, Gb3. To study the relationship of this receptor and toxin effects, globotriaosylceramide was quantitated and further characterized in rabbit small intestinal microvillus membranes at various ages. Glycolipids were extracted from rabbit microvillus membranes, purified on Unisil columns, and quantitated by high-performance liquid chromatography. The major glycolipid peaks were hydroxylated fatty acid-containing glucosylceramide, lactosylceramide, and globotriaosylceramide. There was a marked increase of globotriaosylceramide levels with age, ranging from 0.02 to 16.2 pmol/micrograms microvillus membrane protein in neonates and adults, respectively. The globotriaosylceramide peak was susceptible to alpha-**galactosidase** treatment, which produced an elevation in the lactosylceramide peak, but markedly **reduced globotriaosylceramide** content in 34-day-old rabbits. Binding of iodinated Shiga toxin to globotriaosylceramide was documented on high-performance thin-layer chromatography plates by autoradiography. The glycolipid receptor for Shiga toxin in rabbit microvillus membranes is

thus a hydroxylated fatty acid-containing globotriaosylceramide. This moiety is virtually absent in neonates and gradually increases with age. Quantitative differences in globotriaosylceramide may be the underlying basis for the age-specific differences in functional responsiveness of rabbit intestinal tissue to Shiga toxin.

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=> d au ti so 20-31 l12

L12 ANSWER 20 OF 31 MEDLINE on STN DUPLICATE 14
AU Takenaka T; Murray G J; Qin G; Quirk J M; Ohshima T; Qasba P; Clark K; Kulkarni A B; Brady R O; Medin J A
TI Long-term enzyme correction and lipid reduction in multiple organs of primary and secondary transplanted Fabry mice receiving transduced bone marrow cells.
SO Proceedings of the National Academy of Sciences of the United States of America, (2000 Jun 20) 97 (13) 7515-20.
Journal code: 7505876. ISSN: 0027-8424.

L12 ANSWER 21 OF 31 MEDLINE on STN DUPLICATE 15
AU Abe A; Gregory S; Lee L; Killen P D; Brady R O; Kulkarni A; Shayman J A
TI **Reduction** of **globotriaosylceramide** in Fabry disease mice by substrate deprivation.
SO Journal of clinical investigation, (2000 Jun) 105 (11) 1563-71.
Journal code: 7802877. ISSN: 0021-9738.

L12 ANSWER 22 OF 31 MEDLINE on STN DUPLICATE 16
AU Abe A; Arend L J; Lee L; Lingwood C; Brady R O; Shayman J A
TI Glycosphingolipid depletion in fabry disease lymphoblasts with potent inhibitors of glucosylceramide synthase.
SO Kidney international, (2000 Feb) 57 (2) 446-54.
Journal code: 0323470. ISSN: 0085-2538.

L12 ANSWER 23 OF 31 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AU Shayman, James A. [Reprint author]; Abe, Akira [Reprint author]; Gregory, Susan [Reprint author]; Killen, Paul D.; Brady, Roscoe O.; Kulkarni, Ashok
TI **Reduction** of **globotriaosylceramide** in Fabry disease mice by substrate deprivation.
SO Journal of the American Society of Nephrology, (September, 2000) Vol. 11, No. Program and Abstract Issue, pp. 414A. print.
Meeting Info.: 33rd Annual Meeting of the American Society of Nephrology and the 2000 Renal Week. Toronto, Ontario, Canada. October 10-16, 2000. American Society of Nephrology.
CODEN: JASNEU. ISSN: 1046-6673.

L12 ANSWER 24 OF 31 MEDLINE on STN DUPLICATE 17
AU Schiffmann R; Murray G J; Treco D; Daniel P; Sellos-Moura M; Myers M; Quirk J M; Zirzow G C; Borowski M; Loveday K; Anderson T; Gillespie F; Oliver K L; Jeffries N O; Doo E; Liang T J; Kreps C; Gunter K; Frei K; Crutchfield K; Selden R F; Brady R O
TI Infusion of alpha-**galactosidase** A **reduces** tissue **globotriaosylceramide** storage in patients with Fabry disease.
SO Proceedings of the National Academy of Sciences of the United States of America, (2000 Jan 4) 97 (1) 365-70.
Journal code: 7505876. ISSN: 0027-8424.

L12 ANSWER 25 OF 31 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
AU Cheng, S. H. [Reprint author]; Li, C. [Reprint author]; Ziegler, R. [Reprint author]; Desnick, R. J.; Ioannou, Y. A.; Yew, N. S. [Reprint author]
TI Genetic modification of the liver and lung as portals for delivery of alpha-**galactosidase** into circulation for Fabry disease.
SO Journal of Inherited Metabolic Disease, (July, 2000) Vol. 23, No. Supplement 1, pp. 223. print.
Meeting Info.: VIIIth International Conference on Inborn Errors of Metabolism. England, Cambridge, UK. September 13-17, 2000.
CODEN: JIMDDP. ISSN: 0141-8955.

L12 ANSWER 26 OF 31 CAPLUS COPYRIGHT 2004 ACS on STN
AU Ziegler, Robin J.; Yew, Nelson S.; Li, Chester; Cherry, Maribeth;

Berthelette, Patricia; Romanczuk, Helen; Ioannou, Yiannis A.; Zeidner, Kenneth M.; Desnick, Robert J.; Cheng, Seng H.
TI Correction of enzymatic and lysosomal storage defects in Fabry mice by adenovirus-mediated gene transfer
SO Human Gene Therapy (1999), 10(10), 1667-1682
CODEN: HGTHE3; ISSN: 1043-0342

L12 ANSWER 27 OF 31 MEDLINE on STN DUPLICATE 18
AU Mobassaleh M; Gross S K; McCluer R H; Donohue-Rolfe A; Keusch G T
TI Quantitation of the rabbit intestinal glycolipid receptor for Shiga toxin. Further evidence for the developmental regulation of globotriaosylceramide in microvillus membranes.
SO Gastroenterology, (1989 Aug) 97 (2) 384-91.
Journal code: 0374630. ISSN: 0016-5085.

L12 ANSWER 28 OF 31 MEDLINE on STN
AU Taki T; Maeda H; Arai K; Matsumoto M; Kon K; Ando S
TI Appearance of a novel type of ganglioside (GD1 alpha) in a differentiation-resistant clone of mouse myeloid leukemia cells, M1-R1.
SO Cell structure and function, (1988 Feb) 13 (1) 61-72.
Journal code: 7608465. ISSN: 0386-7196.

L12 ANSWER 29 OF 31 MEDLINE on STN
AU Desnick R J; Dean K J; Grabowski G A; Bishop D F; Sweeley C C
TI Enzyme therapy XVII: metabolic and immunologic evaluation of alpha-**galactosidase** A replacement in Fabry disease.
SO Birth defects original article series, (1980) 16 (1) 393-413.
Journal code: 0003403. ISSN: 0547-6844.

L12 ANSWER 30 OF 31 MEDLINE on STN DUPLICATE 19
AU Svennerholm L; Vanier M T; Mansson J E
TI Krabbe disease: a galactosylsphingosine (psychosine) lipidosis.
SO Journal of lipid research, (1980 Jan) 21 (1) 53-64.
Journal code: 0376606. ISSN: 0022-2275.

L12 ANSWER 31 OF 31 MEDLINE on STN DUPLICATE 20
AU Desnick R J; Dean K J; Grabowski G; Bishop D F; Sweeley C C
TI Enzyme therapy in Fabry disease: differential in vivo plasma clearance and metabolic effectiveness of plasma and splenic alpha-**galactosidase** A isozymes.
SO Proceedings of the National Academy of Sciences of the United States of America, (1979 Oct) 76 (10) 5326-30.
Journal code: 7505876. ISSN: 0027-8424.

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L12 ANSWER 29 OF 31 MEDLINE on STN
AB A pilot trial of enzyme replacement using splenic and plasma forms of alpha-**galactosidase** A was undertaken in 2 brothers with Fabry disease, an X-linked glycosphingolipid storage disease. Partially purified preparations of alpha-**galactosidase** A from human spleen and plasma Cohn fraction IV-1 were prepared aseptically for in vivo administration. The disappearance of enzymatic activity from plasma, levels of circulating substrate, and potential immune response were evaluated following IV administration of 6 unentrapped doses (2,000 U/kg) of each enzyme form to the respective recipient during a 117-day period. Repeated injections were well tolerated. The circulating half-life of the splenic form was about 10 min whereas that for the plasma form was approximately 70 min. No immune response was detected by skin and immunodiffusion tests or by alterations in the maximal activity or clearance kinetics for either enzyme following successive administrations. After each dose of the splenic form, the concentration of the accumulated circulating substrate **globotriaosylceramide**, **decreased**

maximally (approximately 50% of initial values) in 15 min and returned to preinfusion levels by 2-3 hr. In marked contrast, injection of the plasma form decreased the circulating substrate levels 50-70% by 2-6 hr; the concentrations of globotriaosylceramide gradually returned to preinfusion values by 36-72 hr. Two consecutive doses of the plasma form, administered on days 1 and 3, reduced the circulating substrate concentration to normal levels. Prior to the 6th enzyme administration, circulating substrate was stable-isotope labeled by the infusion of dideutero-glucose, and the effects of each enzyme form on circulating substrate degradation and reaccumulation were determined. The results of this study indicated that labeled (newly synthesized) substrate reaccumulated following injection of the splenic enzyme whereas both unlabeled (previously stored?) and labeled substrate reaccumulated in the circulation after administration of the plasma form. These studies demonstrated the differential disappearance kinetics of the splenic and plasma forms of alpha-**galactosidase** A, their differential effects on circulating substrate degradation and reaccumulation, as well as the lack of an immune response to repeated administrations of these homologous, unentrapped enzymes.

L12 ANSWER 31 OF 31 MEDLINE on STN DUPLICATE 20

AB A pilot trial of enzyme replacement with splenic and plasma alpha-**galactosidase** A (alpha-D-**galactosidase**; alpha-D-galactoside galactohydrolase, EC 3.2.1.22) isozymes was undertaken in two brothers with Fabry disease, an X-linked glycosphingolipid storage disease. Six unentrapped doses (2000 units/kg) of each isozyme were administered intravenously to the respective recipients during a 117-day period. The circulating half-life of the splenic isozyme was about 10 min, whereas that for the plasma isozyme was approximately 70 min. No immune response was detected by skin and immunodiffusion tests or by alterations in the maximal activity or clearance kinetics for either isozyme after successive administrations. After each dose of the splenic isozyme, the concentration of the accumulated circulating substrate, trihexosylceramide (**globotriaosylceramide**), **decreased** maximally (approximately 50% of initial values) in 15 min and returned to preinfusion levels by 2-3 hr. In marked contrast, injection of the plasma isozyme decreased the circulating substrate levels 50-70% by 2-6 hr; the concentrations gradually returned to preinfusion values by 36-72 hr.

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